REMARKS

35 USC Section 103

Applicants respectfully request reconsideration of the rejection of the claims as obvious over the four-way combination of Goodey et al., Fogler, Levesque et al., and Costa et al.; and in Rejections # 2-7, further in view of additional references.

Claim 40 is directed to a microfabricated device for fragmenting nucleic acids and requires an inlet, an outlet, and a fragmentation cell having a top wall, bottom wall, and side walls which extend from the top wall to the bottom wall. The side walls taper inwardly to meet the inlet port. In claim 44, the outlet port comprises a constriction having a width in the range of from 1 to 100 μm.

The Office has failed to set forth a *prima facie* case of obviousness because the primary cited references are too remote to be analogous art. And, even if the art were analogous, there are no *reasons* to make the proposed combinations as required by law as articulated in *KSR* and the MPEP; moreover, the references teach away from the proposed combination; and in fact the Office has failed to articulate any reasoning with rational underpinning to support the four-way combination of references.

I. Non-Analogous Art: Fragmentation of Nucleic Acids Versus Multianalyte Sensor Arrays and Continuous-Stirred Tank Reactors

> In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The primary references relied upon by the Office are not

analogous art because the references are completely unrelated to the applicants' field of endeavor -- microfabricated devices for fragmentation of nucleic acids -- and are wholly unrelated to the particular problem with which applicants were concerned -- mechanically fragmenting nucleic acids. The Office's determination of the relevant field of endeavor is impermissibly made without a requisite showing of substantial evidence by reference to the present application:

> ...test for analogous art requires the PTO to determine the appropriate field of endeavor ***by reference to explanations of the invention's subject matter in the patent application, including the embodiments, function, and structure of the claimed invention.***
>
> *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

The assessment of the field of endeavor is not a subjective call for the examiner. *Id.* at 1326. The PTO must support a factual assessment of field of endeavor with "substantial evidence." *Id.*

As an example, the Federal Circuit reversed a finding of obviousness because a reference could not "be considered to be within [the inventor's] field of endeavor merely because both relate to the petroleum industry." *In re Clay*, 966 F.2d 656, 660 (Fed. Cir. 1992). Clay's invention was a process of storing refined liquid hydrocarbon in a storage tank having a dead volume and displacing the liquid from the tank using a gel. *Id.* at 657, 659. The reference at issue, Sydansk, was directed to a process for reducing the permeability of hydrocarbon-bearing formations and thus improving oil production, using a gel similar to that in Clay's invention. *Id.* at 658. The PTO argued that Sydansk and Clay's inventions were part of a common endeavor -- "maximizing withdrawal of petroleum stored in petroleum reservoirs." *Id.* at 659. The Federal Circuit, however, found the Board clearly erred in making this broad categorization. The Federal Circuit

compared function and structure:

> Sydansk teaches the use of a gel in unconfined and irregular volumes within generally underground natural oil-bearing formations to channel flow in a desired direction; Clay teaches the introduction of gel to the confined dead volume of a man-made storage tank. *Id.*

Accordingly, the court determined Clay's field of endeavor was "*storage* of refined liquid hydrocarbons," compared to Sydansk's field of endeavor of "*extraction* of crude petroleum."

Reference to the present application clearly indicates the field of endeavor of applicants' invention is microfabricated devices for fragmentation of nucleic acids. The title of the present application is "A Microfabricated Fluidic Device for Fragmentation." As stated in sentence 1, lines 1 and 2 of paragraph 0001, "The present invention relates to a microfluidic device for nucleic acid fragmentation." The application goes on to explain the background purposes for fragmentation of DNA and RNA. See, e.g., paragraphs 0002 and 0003. The application also specifically explains the structure of the device as being microfabricated. See, e.g., paragraph 0004. All of the embodiments described in the application show microfabricated devices relating to fragmentation of nucleic acids. The preamble of claim 40, the only independent claim, recites a "microfabricated device for fragmenting nucleic acids." The structure of applicants claimed invention is clearly microfabricated, and the function of applicants' invention is clearly to fragment nucleic acids. Therefore, the field of applicants' invention is microfabricated devices for fragmentation of nucleic acids. Not one of the cited references is in this field.

Turning to the Office's present reasoning, the Office makes three statements regarding the field of endeavor of Goodey et al. as it relates to applicants' invention. First, the Office states

"both Goodey et al. and the instant application are drawn to reactor systems for shearing polymers." In the next paragraph, when discussing Goodey et al. and an additional reference, the Office states "Goodey et al. [is] analogous because [it] relate[s] to reactor systems for housing reactions." Finally, when considering Goodey et al. with the other three references of the four-way combination, the Office states "all of the prior art relates to reactor systems for the analysis of molecules." So the Office treats the field of endeavor as a fleeting concept, changing it from "shearing polymers" to "housing reactions" to "analysis of molecules." And not only is the concept as characterized impermissibly malleable, it ignores the relevant technical specifics of the claimed invention.

These statements of field of endeavor are improperly broad and subjective. For example, "reactor systems for housing reactions" encompasses nuclear reactors, kilns, microwave ovens, and test tubes. None of the stated fields of endeavor is reasonably tailored. The Office provides no evidence such as references to the present application to support these conclusions of field of endeavor. As evidenced by the Office's amorphous and malleable categorization of applicants' field of endeavor -- first, reactor system for shearing polymers; second, reactor systems for housing reactions; and third, reactor systems for the analysis of molecules -- the Office is applying convenient and subjective definitions of the field of applicants' endeavor. For the Office, applicants' field is a "moving target." The field of applicants' endeavor cannot fairly be variable based upon the particular reference the Office wishes to apply. As explained above, according to an analysis well supported factually by the present application with references to the embodiments, function, and structure of the claimed invention, applicants' field of endeavor is properly defined as microfabricated devices for fragmentation of nucleic acids.

The field of endeavor of Goodey et al. -- analysis of

complex fluids using multianalyte sensor arrays -- is wholly unrelated to applicants' field of endeavor. According to the title of Goodey et al., the reference is directed to "Development of Multianalyte Sensor Arrays Composed of Chemically Derivatized Polymeric Microspheres Localized in Micromachined Cavities." Upon referencing sections of Goodey et al. such as the "Abstract," "Introduction," "Materials," "Fabrication of the Micrbead Arrays," and "Results and Discussion," it is clearly evident that the structure of Goodey et al.'s sensor arrays, as shown in Figs. 1 and 2 of page 2563, includes microspheres immobilized or confined in a pyramidal "pit" having side walls that taper inward to the outlet of the pit so that the top-to-bottom flow direction of fluid to be analyzed forces the beads to the lower region of the pit, which serves as a self-centering aid. See, e.g., page 2563, bottom column 2. The function of Goodey et al. is to include several of these microspheres immobilized in pits on a "taste chip" to provide a "chip-based system suitable for the analysis of complex fluids" via "solution-phase multianalyte detection." Page 2562, middle column 2. Thus, the field of endeavor of Goodey et al. is analysis of complex fluids using multianalyte sensor arrays. The disparity between applicants' and Goodey et al.'s respective fields of endeavor is much greater than the difference in *Clay* between storage of refined liquid hydrocarbons and extraction of crude petroleum, which required the Federal Circuit to reverse the Board.

Moreover, the Office's statement that Goodey et al. is drawn to a "reactor system[] for shearing polymers" is factually incorrect. As explained above, Goodey et al. is directed to flowing complex fluids such as beverages and biological samples over a microbead sensor array for analysis of pH, metal cations, sugars, and antibodies within the fluids. See page 2560, bottom column 2. There is no suggestion of any shearing. Accordingly, Goodey et al. in fact do not disclose a reactor system for

shearing polymers.

Moreover, addressing the second prong of the *Oetiker* analysis, Goodey et al. is also wholly unrelated to the particular problem with which applicants were concerned. The case law provides guidelines for determining the reasonable pertinence of a reference to the problem with which the inventor was concerned. According to the Federal Circuit, "the purposes of both the invention and the prior art are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve." *Clay*, 966 F.2d at 659. If a reference is directed to a different purpose, the inventor would not have considered it. *Id.*

In *Clay*, for example, Sydansk was faced with the problem of recovering oil from rock, a matrix of porous, permeable sedimentary subterranean formation. *Id.* The purpose of Sydansk's gel treatment of underground formations was to "fill anomalies so as to improve flow profiles and sweep efficiencies of injection and production fluids through a formation, while Clay's gel function[ed] to displace liquid product from the dead volume of a storage tank." *Id.* The Federal Circuit determined Clay was concerned with the problem of "preventing loss of stored product to tank dead volume while preventing contamination of such a product." *Id.* at 659-60. The Federal Circuit reversed the Board because a "person having ordinary skill in the art would not reasonably have expected to solve the problem of dead volume in tanks for storing refined petroleum by considering a reference dealing with plugging underground formation anomalies." *Id.* at 660.

The particular problem applicants were concerned with was random fragmentation of nucleic acids by mechanical force. Paragraph 0002. The purpose of applicants' device is to provide fragmented nucleic acid samples for use in, for example, "a nucleic acid sequence amplification and detection process" for

"nucleic acid analysis or genomic library generation." Paragraphs 0001 and 0002. Goodey et al. is directed to solving a vastly different problem compared to Applicants' invention. Goodey et al. is directed to the problem of analyzing mulitanalyte mixtures to enable intelligent, rapid, and accurate decisions related to the chemical composition of solution-phase samples. Page 2560, middle column 2. The purpose of Goodey et al. is to provide an automated "total analysis system" that is "capable analysis of pH, metal cations, sugars, and antibodies within complex fluids such as beverages, and biological samples." Page 2560, bottom column 2. As Goodey et al. explain in detail:

> For many important medical, process control, environmental, food safety, and food/beverage processing applications, the identification of analytes that are difficult to volatize without decomposition is essential. For these areas, the need for a chemically diverse, solution-phase multianalyte detection system is acute. Here the challenges associated with distinguishing between subtle differences in common electrolytes (Na^+ vs K^+ and Mg^{2+} vs Ca^{2+}), small differences in acidity (citric acid vs lactic acid), slight changes in protein structures (influenza AA vs influenza B, and complex sugar isomers (glucose vs galactose) makes the development of chemically diverse solution multianalyte detection arrays a very complex issue.

Page 2560, middle column 1. Simply stated, a person having ordinary skill in the art would not reasonably have expected to solve the problem of accomplishing random fragmentation of nucleic acids by mechanical force by considering a reference dealing with multianalyte sensor arrays composed of chemically derivatized polymeric microspheres. The gap between the problems addressed by applicants' device and Goodey's sensor arrays is far greater than the gap between the problems faced in *Clay* -- dead volume in tanks for storing refined petroleum and plugging underground formation anomalies -- which the Federal Circuit determined required reversal of the Board. Goodey et al. is clearly unrelated to the particular problem with which applicants

were concerned.

The Office also has failed to show that Fogler is in the field of applicants' endeavor or reasonably pertinent to the particular problem with which the applicants were concerned. The Office states "Fogler [is] analogous because [it] relate[s] to reactor systems for housing reactions" and that all of the prior art relates to reactor systems for the analysis of molecules. As explained above, these fields of endeavor are overly broad and subjective. The Office cannot reasonably believe these are fair categorizations of the field of applicants' endeavor.

The field of Fogler's endeavor -- catalytic or fluid-solid reactors -- is completely different from microfabricated devices for fragmentation of nucleic acids. The Office relies on Fig. 6-16, which shows a perfectly mixed fluidized continuous-stirred tank reactor (CSTR). Page 270. As is evident from the name CSTR, the function of this reactor is to provide "perfect mixing behavior" to facilitate a catalyzed chemical reaction. See page 272. Regarding structure, CSTRs are of much larger scale than microfabrication devices. As described above, the field of applicants' endeavor is microfabricated devices for fragmentation of nucleic acids. The function of applicants' invention is to mechanically fragment nucleic acids. Neither the function nor structure of the CSTR in Fogler is at all similar to the function or structure of applicants' microfabricated nucleic acid fragmenting device. In particular, the irrelevance of Fogler is underscored by the fact that applicants' device is microfabricated, as clearly explained in the specification in, for example, paragraph 0004, compared to the much larger scale of CSTRs. *See, e.g., Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 864-65 (Fed. Cir. 1993) (reversing a finding of obviousness based on non-analogous art where the reference at issue disclosed a "module [that] was developed for use in a controller of large industrial machinery and could not be used in a personal computer," for which the inventor's compact device was designed).

The CSTR of Fogler is clearly outside the field of applicants' endeavor.

Moreover, the problem addressed by Fogler is unrelated to the particular problem which was faced by applicants. Fogler's CSTR addressed the problem of, for example, achieving continuous homogenous mixing to promote maximum fluid-to-solid contact to facilitate catalytic reactions. Applicants' particular problem was mechanically fragmenting amino acids. A person having ordinary skill in the art would not reasonably have expected to solve the problem of accomplishing fragmentation of nucleic acids by mechanical force by considering a reference dealing with facilitating fluid-solid chemical reactions. Therefore, Fogler is wholly unrelated to the particular problem with which applicants were concerned.

In view of the foregoing, all of the rejections should be withdrawn because neither Goodey et al. nor Fogler are analogous prior art.

II. Even if the Art Were Analogous, There Is No Reason to Make the Proposed Combination, and the Proposed Combination Does Not Lead to the Device of Applicants' Claim 40

Applicants' claim 40 is directed to a microfabricated device for fragmenting nucleic acids in a fluid, and has these express claim requirements:

> a) a fragmentation cell, an inlet port, and an outlet port;
>
> b) the outlet port is dimensioned to impede the flow of a fluid sample out of the cell so as to effect shearing of nucleic acids molecules;
>
> c) a chamber of the fragmentation cell having a top wall in which is formed the inlet port, a bottom wall in which is formed the outlet port, and side walls; and

d) the side walls taper inwardly to meet the inlet port.

The express requirement that the sidewalls taper inwardly to meet the inlet port is described at length in the specification and is a critical feature of the invention:

The side walls portions next to or adjacent the inlet port advantageously subtend an angle of less than 90 degrees to the longitudinal axis of the inlet port. Such a gradual opening allows for substantially bubble-free filling of the cell.

Paragraph [0019] of published application 2006/0057581

FIG. 1 (a) shows a scanning electron micrograph (SEM) of a fragmentation cell 1 (or shearing unit), one in a connected series made by deep reactive-ion etching (DRIE) in silicon. The constriction outlet 10 (approx. 75 μm long) is designed to have an abrupt change in cross-section from large to small in the flow direction. ***At the chamber inlet 20, a gradual opening has been found to help avoid air bubbles being trapped in the structure***. The constriction width (i.e. the width of the outlet and inlet) is approx. 25 μm and the feature depths approx. 50 μm.

Paragragh [0072] of published application 2006/0057581

The shape of fragmentation cell 1 may be described as an irregular hexagon with an essentially straight bottom wall 5 in which the outlet 10 is formed at approximately the mid point. It can be seen that the bottom wall 5 is substantially perpendicular to the longitudinal axis of the outlet 10 (and the direction of flow). Thus, the bottom wall 5 subtends an angle of approximately 90 degrees to the longitudinal axis of the outlet 10 (and the direction of flow). The bottom wall 5 is adjacent and substantially perpendicular to two lower side wall portions 15a and 15b. The upper portions 15c and 15d of the side walls taper inwardly to meet the inlet 20 at the top of the cell 1. ***Thus, upper side walls portions 15c and 15d***

> ***each subtend an angle of less than 90 degrees to the longitudinal axis of the inlet (and the direction of flow).*** It can be seen, however, that the uppermost side wall portions 15e and 15f immediately adjacent the inlet 20 subtend an angle of approximately 90 degrees to the longitudinal axis of the inlet 10 (and the direction of flow). It can also be seen that the cell 1 is asymmetric about the horizontal axis and substantially symmetric about the longitudinal axis (the longitudinal axis is essentially coincident with the direction of flow).
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> Paragragh [0073] of published application 2006/0057581

For the reasons stated below, incorporating this tapering feature cannot fairly be deemed to have been obvious from the cited references or general knowledge in the art, even if these references were -- improperly -- deemed to be analogous art.

In asserting *prima facie* obviousness, the Office bears an initial burden of articulating ***reasons*** why one skilled in the art would have selected the particular elements of Goodey et al., Fogler et al., Costa et al. and Levesque et al. and combined them in the manner proposed:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)
>
> A rejection for obviousness must include articulated reasoning with some rational underpinning to support the legal conclusion." *KSR* at 418., quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

The Office acknowledges that Goodey et al. do not disclose side walls tapering inwardly to meet the inlet port or the use of the device to shear nucleic acids. The Office then asserts on page 9 of the action that it would have been obvious to modify Goodey et al.'s device with the tapered walls of Fogler. But not

one of the three "reasons" recited by the Office on page 9 supports this conclusion.

Statement I. "It would have been obvious ... because it is obvious to substitute known elements in the prior art to yield predictable results."

This statement is circular: "it is obvious ... because it is obvious." This is nothing more than a legal conclusion. This does not constitute "articulated reasoning" with "rational underpinning" which the MPEP and *KSR* decision emphasize the law requires. Indeed Goodey et al.'s reactor is a "known element"; and so are Fogler et al.'s "tapered walls." But here there is no basis upon which to predict any result of the proposed modification, much less any reason to make the proposed modification. Goodey et al.'s device is a "Multianalyte Sensor Array Composed of Chemically Derivatized Polymeric Microspheres" which was developed to assay "multifunctional fluids" (p. 2560, column 1), i.e., figure out what a particular fluid contains. It is related to electronically analyzing the taste and smell of fluids (p. 2560, column 2). Fogler's device is a fluidized continuous-stirred tank reactor (CSTR) described on page 272 as "a catalytic or fluid-solid reactor." Fogler does not discuss what the purpose is for tapering toward the inlet, if any. Nor does Fogler discuss what the result is of tapering toward the inlet. There is simply no basis to conclude that there would be any predictable or desirable result achieved by modifying Goodey et al.'s taste analyzer with this feature of Fogler's stirred tank reactor. Not only does Fogler not state what results from his inlet tapering in his stirred tank reactor, but there is moreover no basis to predict what results such tapering would have on Goodey et al.'s taste analyzer. This is especially true considering what disparate devices Fogler's stirred tank reactor is from Goodey et al.'s taste analyzer. Accordingly, the

Office's statement that "It would have been obvious . . . because it is obvious to substitute known elements in the prior art to yield predictable results" provides zero support for the Office's conclusion of obviousness.

Statement II. "In this instance, the tapered reactor in Fogler is an alternative to the reactor in Goodey et al."

Any substitution is, of course, an "alternative," so this sentence does not add anything to the analysis. Most importantly, here the Office does not provide any reason why it would have been obvious to implement this alternative. That something is an alternative does not make it an obvious modification. Why is it a *practical* alternative? Why would one skilled in the art infer interchangeability? Fogler discloses a continuous stirred tank reactor. Goodey et al. discloses a device for analyzing taste/smells. There is no reason of record why tapers in CSTRs are known alternatives for anti-tapers in chambers of smell analyzers. And in fact there is no basis for concluding this significant of a feature from a stirred tank reactor would be a suitable alternative for the walls in Goodey et al.'s disparate taste/smell analyzer, which in fact taper in the directly opposite orientation for the express purpose of forcing the beads against the outlet.

Statement III. "There would have been a reasonable expectation of success in combining Goodey et al. with Fogler because both are reactor systems used for manipulating polymers."

The fact that two things are reactor systems used for manipulating polymers does not mean that there would be any reasonable expectation of success. An assessment of whether there would be any reasonable expectation of success cannot be made in a vacuum. This inquiry only has meaning in the context

of a particular goal and prospects for "success" of achieving that goal. Goodey et al.'s cited component is a chamber of a device for analyzing smells. There is no information given in the Office action as to what effect reversing the taper of the side walls would have on the chamber's effectiveness in the smell-analyzing device. In fact, one would reasonably infer from Goodey et al.'s goal of forcing microbeads against the outlet that reversing the taper would defeat this goal. So there is no basis for reaching any conclusion about the prospects for success.

Accordingly, all three of these statements which the Office advances as "reasons" to make the hindsight modification are conclusory statements, wholly devoid of any explicit analysis, and contrary to technical reasoning. The Office does not state what predictable results the combination of Goodey et al. and Fogler would provide, nor does the Office state what success is reasonably expected by the combination. The statements of predictability, alternatives, and expectations are merely overly broad statements of relation; they are not *reasons* to combine.

Applicants therefore respectfully submit that the Office's proposed "reasons" are not really "reasons" at all, and the rejection is deficient.

More important than the deficient analysis provided by the Office, however, is that it is in fact evident that no person having ordinary skill in the art and common sense would modify the chamber of Goodey et al. to have Fogler's side walls tapered to the inlet port. In fact, Goodey et al. teach away from such a configuration. Goodey et al. disclose side walls that taper inwardly to meet the outlet port, not to meet the inlet port. This configuration is provided for a specific and important reason. As explained above, the Goodey et al. reference is directed to flowing complex fluids such as beverages and biological samples over a microbead sensor array for analysis of pH, metal cations, sugars, and antibodies within the fluids.

Goodey et al. emphasize the importance of "strategic placement" of the sensor, more specifically the microbead sensor or polymeric microsphere, for proper fluid flow over the sensor. As explained in the caption for Figure 2, there is shown a section of a "bead confinement strategy":

> Using the stated top-to-bottom flow direction, the beads become forced to the lower region of the cell and under these circumstances the pyramidal pits serve as self-centering aids. Goodey et al.; page 2563, bottom column 2.

Goodey et al. describe the beads as "immobilized" numerous times, e.g.:

> Immobilizing the polymer beads within the cavities in the chips allows for the full advantage of polymer swelling, while avoiding the problems incurred by attaching the polymer to a platform. Goodey et al. page 2563, col. 1

Modifying the cavity to have side walls tapered to the inlet port would cause turbulence tending to mobilize or unseat the sensors. This would render Goodey et al. inoperable for its intended purpose. As provided by MPEP §2143.10(V):

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Nor is there any KSR-required *reason* to change the tapering in the Goodey et al. device, because to do so would disembowel it of its function and goal - to securedly seat the microbeads against the outlet. In *Gordon* -- which is on all fours with the present situation -- the Board had concluded that a claimed blood filter assembly would have been produced by simply turning the

prior art oil strainer upside down. However, the Federal Circuit concluded that the proposed inversion would have rendered the prior art device inoperable, so that obviousness could not fairly be established on the basis the Board proposed. The Office's current proposal to invert Goodey et al.'s tapering is similarly unreasonable, inappropriate, and not sustainable.

In addition, to incorporate tapering toward Goodey et al.'s inlet would effectively decrease the opening of the cavity, which Goodey et al. explain "complicates the bead placement issue." Column 2, page 2562. Accordingly, a person having ordinary skill in the art would have no reason to modify and would in fact be discouraged from modifying Goodey et al. to incorporate Fogler's side walls tapered inward to the inlet port.

The Office further states that it "would have been obvious to modify devices of Goodey et al. and Fogler et al. by use of the cellular shearing device of Levesque et al. . . . because it is obvious to substitute known elements in the prior art to yield a predictable result." Again, this reasoning is circular and conclusory. Of course Levesque et al.'s elements are known and so are Goodey et al.'s. But whatever Levesque et al. disclose to accomplish shearing cannot fairly be deemed to have a predictable impact on Goodey et al.'s disparate taste/smell analyzer, which is not intended for shearing.

Moreover, the Office fails to explain how the combination of Goodey et al. and Fogler would be modified to incorporate the "cellular shearing device" of Levesque et al. As shown in Figure of page 341, the "cellular shearing device" of Levesque et al. is a chamber having parallel walls that result in steady, uniform laminar flow. The Office is suggesting that the combination of Goodey et al. and Fogler should be modified to have parallel walls, and the Office has impermissibly and conveniently selected individual elements without any respect for how they might mechanically impact Goodey et al.'s taste/smell analyzer. At best, this analysis is based on speculation and unfounded

assumptions.

It is evident, in view of a) the disparate nature of the references, b) the failure of either of the primary two references to relate to any sort of fragmentation, and c) the Office's lack of explicit technical reasoning to support the proposed combinations, that the Office has applied impermissible hindsight in making this four-way combination using applicants' claims as a template. Goodey et al., Fogler, Levesque et al., and Costa et al. are so unrelated to each other -- Goodey et al.'s isolating a fluid sample for electronic taste and smell analysis versus Fogler's chemical reaction vessel versus Levesque et al.'s study of hemodynamic forces on vascular endothelial cells versus Costa et al.'s assay for detecting covalent DNA-protein complexes -- that there is absolutely no reason one skilled in the art would incorporate aspects from each of the references of the four-way combination to arrive at the combination of elements explicitly required by claim 40. Moreover, the references teach away from this combination. Claim 40 is therefore respectfully submitted to be patentable over this combination.

Claims 41-77 depend from claim 40 and are therefore respectfully submitted to be patentable for the same reasons as claim 40, further in view of the additional elements they require.

Claim 44, for example, expressly requires that the outlet port comprises a constriction having a width in the range of from 1 to 100 μm. This is an express requirement that cannot be ignored in assessing patentability. This is neither disclosed nor suggested by the references of record, nor would there be any reason to modify the Goodey et al. device to require this dimension.

Inasmuch as all of rejections #1-7 rely on the same combination of these four references, applicants respectfully request withdrawal of all of the rejections.

CONCLUSION

Applicants request issuance of a Notice of Allowability for all pending claims.

Respectfully submitted,

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